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Pharmacokinetics and Safety of Levofloxacin in Patients with Human Immunodeficiency Virus Infection

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Levofloxacin, the bacteriologically active isomer of ofloxacin, has microbiologic activity against many pathogens common in human immunodeficiency virus (HIV)-infected patients, including *Mycoplasma* species which may be cofactors in the progression of HIV disease. The purpose of this phase I, double-blind, randomized (1:1), placebo-controlled trial was to evaluate the pharmacokinetics and safety of levofloxacin hemihydrate in 10 asymptomatic HIV-infected males. Plasma concentrations by chiral high-performance liquid chromatography (HPLC) were evaluated for 48 h after a single 350-mg oral dose, at morning predose during the multiple-dosing phase, and for 72 h at steady state after a week of 350 mg every 8 h orally. Mean ± standard deviation levofloxacin pharmacokinetic parameters (by noncompartmental moment method) after multiple dosing were as follows: area under the concentration-time curve, 31.24 ± 5.60 mg · h/liter; apparent total body clearance, 11.18 ± 1.76 liters/h; renal clearance, 8.63 ± 2.82 liters/h; steady-state volume of distribution, 104.10 ± 12.48 liters; and effective half-life, 6.50 ± 0.51 h. Single-dose parameters were not significantly different from the multiple-dose parameters, with the exception of peak concentrations in plasma, which were 4.79 ± 1.00 and 6.92 ± 1.56 mg/liter for single- and multiple-dose data, respectively. Essentially identical parameter values were obtained from curve-fitting analysis when the entire 13-day plasma concentration profiles of the subjects were analyzed simultaneously by a two-compartmental distribution model. Levofloxacin pharmacokinetics in HIV-infected patients remained linear upon multiple dosing. The dosing regimen studied provides levels in plasma and urine well above those found to be effective in vitro against pathogens common in HIV-infected patients. Levofloxacin was well-tolerated in this group of asymptomatic HIV-infected males; there were no statistically significant differences in adverse effects in the two groups ($P = 0.22$). Use of a placebo control helped to differentiate disease-related adverse effects from those related to the study drug.

Levofloxacin, the bacteriologically active optical isomer (*S*-enantiomer) of ofloxacin, is a broad-spectrum antimicrobial agent currently being developed for the treatment of a variety of bacterial infections (5). This fluoroquinolone antibiotic has potent in vitro activity against many pathogens common in human immunodeficiency virus (HIV)-infected patients, including *Mycoplasma* species, which may be cofactors in the progression of HIV disease (1, 7, 10).

HIV-infected patients may have gastrointestinal infections or alterations in gastrointestinal function which might affect transit time, motility, and drug absorption. Furthermore, patients with HIV infection may experience disease-related adverse events which may be confused with drug side effects. Although these events are more common in patients with advanced disease, patients at all stages of HIV infection, including asymptomatic individuals, may experience HIV-related adverse effects. Therefore, the purpose of this placebo-controlled study was to evaluate the pharmacokinetics and safety of levofloxacin in patients with HIV infection.

MATERIALS AND METHODS

Subjects and study design. Ten asymptomatic HIV-infected males at least 18 years of age with T4 helper lymphocyte counts of at least 200/mm^3 and no history of opportunistic infection or neoplasm were enrolled in this randomized, double-blind, placebo-controlled, parallel, phase I study. Informed consent was obtained from each subject prior to enrollment; the study protocol was approved by the Duke University Medical Center Institutional Review Board. Prior to study enrollment, subjects underwent a review of their medical history, physical examination, and a battery of laboratory tests. Subjects with the following characteristics were excluded: previous allergic or serious reaction to any quinolone antibiotic; presence of any gastrointestinal problem which might interfere with absorption of an oral dosing regimen; significant ophthalmologic, hepatic, cardiovascular, hematologic, neurologic, psychiatric, respiratory, or metabolic disease; creatinine clearance less than 70 ml/min (estimated via the method of Cockcroft and Gault); ethanol or drug abuse; and donation of ≥1 U of blood or acute loss of an equivalent amount of blood within 1 month prior to study entry. Subjects discontinued all medication at least 72 h prior to study drug administration.

After screening, eligible subjects reported to the Duke University Clinical Research Unit the evening prior to study drug administration, where they remained sequestered until the completion of study procedures on day 13. Subjects refrained from ingesting alcoholic beverages, caffeine, methylxanthine-containing foods and beverages, and antacids from 48 h prior to the study until the conclusion of the sequestration period. A diet devoid of these substances was served to study participants by the research unit dietary staff.

After an overnight fast, subjects were randomized (1:1) to receive a single 350-mg oral dose of levofloxacin hemihydrate

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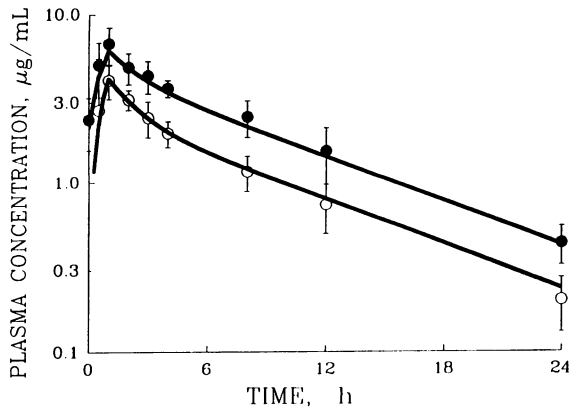

FIG. 1. Mean C_ps of levofloxacin following single (○ [day 1]) and multiple (● [day 10]) 350-mg oral doses of levofloxacin hemihydrate to asymptomatic HIV-infected patients. Boldface lines represent fitted curves from the pharmacokinetics model.

or an identical-appearing placebo. Venous blood samples (5 ml) for determination of plasma levofloxacin concentrations were obtained at 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12.0, 24.0, 36.0, and 48.0 h. On the morning of study day 3, subjects began taking multiple doses of the study drug to which they were originally randomized (350 mg of levofloxacin hemihydrate or an identical placebo orally every 8 h) and continued study drug administration until the morning of day 10. Trough blood samples were obtained immediately prior to the morning dose on study days 4, 6, 7, 8, 9, and 10. Subjects took the final dose of study medication on the morning of day 10 and underwent a plasma pharmacokinetic sampling sequence similar to that on study day 1 with the addition of a 72-h blood sample. Blood collected for plasma harvest in a Venoject tube was centrifuged for at least 10 min at 2,000 rpm. The plasma was then removed via a disposable Pasteur pipette and placed into a plastic tube for freezing at −70°C until the time of sample analysis.

Urine samples for analysis of levofloxacin were collected beginning 8 h prior to the first dose and continuing at the following intervals: 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 h. In addition, urine samples were collected on day 10 after the last dose of study medication according to the following sequence: 0 to 2, 2 to 4, 4 to 8, 8 to 24, and 24 to 48 h. After collection, the total urine volume and pH of each collection were recorded, and a 100-ml aliquot was measured and frozen at −70°C until the time of sample analysis.

On study day 11, subjects underwent safety laboratory testing (hematology, serum chemistry, urinalysis) and a physical examination. Subjects were discharged from the research unit following the final sample collection on study day 13.

Analytical methodology. Concentrations of levofloxacin in plasma and urine were determined by a sensitive, specific, chiral high-performance liquid chromatography (HPLC) method previously described (6). Resolution of ofloxacin isomers was accomplished through the formation of the diastereoisomeric salts with L-leucinamide by a two-step chemical reaction. After extraction of levofloxacin from the sample matrix with dichloromethane at pH 7, the amide was formed by addition of diphenylphosphinyl chloride, triethylamine, and L-leucinamide. The salt was then extracted from the reaction medium with 1 N HCl, injected onto a C_{18} column, and eluted by a mixture consisting of 20% acetonitrile and 80% 0.2 M tetraethylammonium phosphate buffer (pH 1.85). Detection and quantitation were accomplished by an on-line fluorescence detector (excitation wavelength, 298; emission wavelength, 458) coupled with a Hewlett-Packard HP 3350 minicomputer through an A/D converter. The ethyl analog of levofloxacin, 9-fluoro-2,3-dihydro-3-methyl-10(4-ethyl-1-piperazinyl)-7-oxo-7H-pyrido-[1,2,3,-de][1,4]benzoxazine-6-carboxylic acid, was used as the internal standard. Assay conditions for the urine samples were the same as those for plasma samples, with the exception of volumes aliquoted (plasma, 0.5 ml of plasma and 2 ml of pH 7 buffer; urine, 0.01 ml of urine and 0.1 ml of buffer).

Before study samples were analyzed, the intra- and interday accuracy and precision of the assay method were established by analyzing a series of standard curves and seeded controls on three different days. Interday precision was found to be under 10%, and the interday accuracy was within 15% of the theoretical (seeded) value. The following coefficients of variation were obtained for the plasma concentrations (nanograms per milliliter) listed: 6, 8%; 12, 6%; 24, 3%; 64, 2%; 128, 1%; 255, 5%; 510, 4%; 1,020, 7%. For the urine concentrations (micrograms per milliliter) listed, the following coefficients of variation were obtained: 2, 10%; 3, 4%; 6, 7%; 13, 2%; 25, 1%; 50, 1%; 71, 1%; 100, 1%; 177, 2%; 261, 1%; 354, 4%; 434, 3%; 566, 3%. On each day of study sample analysis, a standard curve consisting of eight concentrations covering the linear range (r^2 of 0.991 to 0.998 for all curves analyzed) of the method (8.2 to 1,048.2 ng/ml for plasma samples and 2 to 1,132 μg/ml for urine samples) was extracted and analyzed. Seeded controls were also analyzed with the unknown study samples. Data were deemed acceptable if the precision of the seeded controls was under 10% and the accuracy of the mean value was within 15% of the theoretical value.

Pharmacokinetic and safety analysis. Levofloxacin absorption, distribution, and elimination were determined after a single dose and at steady state from plasma drug concentra-

TABLE 1. Observed oral absorption parameters of levofloxacin in HIV-infected patients after single- and multiple-dose levofloxacin hemihydrate administration

Subject no.	Single dose (day 1)			Multiple dose (day 10)		
	T_{max} (h)	C_{max} (mg/liter)	C_{min} (mg/liter)	T_{max} (h)	C_{max} (mg/liter)	C_{min} (mg/liter)
101	0.50	5.40	1.11	1.00	7.17	1.73
104	1.00	3.91	0.83	1.00	5.02	2.41
106	1.00	5.19	1.61	1.00	9.27	3.36
107	2.00	3.58	1.09	1.00	6.17	2.56
110	0.50	5.89	1.18	0.50	6.95	2.21
Mean ± SD	1.00 ± 0.61	4.79 ± 1.00	1.16 ± 0.28	0.90 ± 0.22	6.92 ± 1.56[a]	2.46 ± 0.60[a]

[a] Significantly different from the corresponding single-dose values at $P = 0.05$ from paired t test analysis.

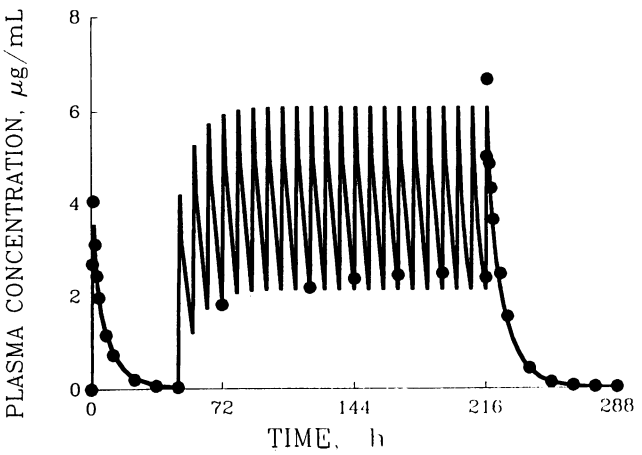

FIG. 2. Observed (●) and predicted (boldface line simulated from pharmacokinetics model fitting) mean C_ps of levofloxacin after multiple 350-mg doses of levofloxacin hemihydrate every 8 h to asymptomatic HIV-infected patients.

tion-time profiles and urine data. The levofloxacin absorption rate, as reflected by the peak concentrations of drug in plasma (C_{max}), and time to reach C_{max} (T_{max}) were estimated by visual inspection of the plasma drug concentration (C_p)-versus-time data. The C_{max}, T_{max}, and trough 8-h postdose concentrations (C_{min}) of the subjects on study days 1 and 10 were compared. Attainment of steady-state conditions on day 10 was evaluated by comparing predose and trough plasma concentrations on study day 10 from the same subjects. Upon demonstration of steady-state conditions on day 10, levofloxacin disposition kinetics were determined, initially by a noncompartmental method from the C_p-versus-time profiles and urinary recoveries on days 1 and 10. The absorption rate was assumed to be zero order and complete at T_{max}. Elimination was assumed to be linear and first order. This model has been successfully applied to characterize the pharmacokinetics of ofloxacin following multiple oral administrations (4). Pharmacokinetic parameters estimated by the moment method included the area under the plasma concentration-time curve (AUC) by trapezoidal summation method; postabsorption mean residence time (MRT), calculated as (AUMC/AUC) − (T_{max}/2); mean effective half-life ($t_{1/2}$), calculated as 0.693 × MRT; apparent total body clearance (Cl_p/F), calculated as dose/AUC; renal clearance (Cl_R), calculated as Au/AUC; and the steady-state volume of distribution (V_{ss}) of levofloxacin, calculated as dose/(AUC × MRT) in subjects after a single dose and at steady-state conditions. AUMC and Au refer to the area under the first moment of the plasma concentration-time curve and the total urinary recovery of levofloxacin at the corresponding AUC intervals, respectively. Cl_R was calculated only where urine collections were complete. AUMC at steady state was calculated according to the method described by Smith and Schentag (11).

To further examine the absorption, distribution, and elimination kinetics of levofloxacin and the consistency of these parameters upon multiple dosing in HIV-infected subjects, the C_p-versus-time profiles of each subject during the 13 days of levofloxacin administration were evaluated simultaneously by a compartmental nonlinear regression method. Equations for one- and two-compartment models with the assumptions of short-term zero-order absorption and first-order elimination processes were employed. Computation was performed via the

TABLE 2. Disposition pharmacokinetic parameters of levofloxacin in HIV-infected patients estimated from noncompartmental moment analysis method

Subject no.	Single dose (day 1)						Multiple dose (day 10)					
	AUC (mg · h/liter)[a]	MRT (h)	$t_{1/2}$ (h)	Cl_p/F (liters/h)	Cl_r (liters/h)	V_{ss} (liters)	AUC (mg · h/liter)	MRT (h)	$t_{1/2}$ (h)	Cl_p/F (liters/h)	Cl_r (liters/h)	V_{ss} (liters)
101	31.1	9.27	6.42	11.0	4.18	102.0	26.1	8.25	5.72	13.1	Sample lost	108.0
104	21.5	7.67	5.32	15.9	15.4	122.0	28.0	9.87	6.84	12.2	12.2	120.0
106	38.7	8.98	6.22	8.82	7.6	79.1	40.6	10.2	7.04	8.41	5.25	85.4
107	24.0	6.75	4.68	14.2	10.3	95.9	30.8	9.18	6.36	11.1	8.54	102.0
110	29.4	8.17	5.66	11.6	4.8	94.8	30.7	9.46	6.56	11.1	8.53	105.0
Mean ± SD	29.94 ± 6.71	8.17 ± 1.02	5.66 ± 0.70	12.3 ± 2.78	8.46 ± 4.60	98.76 ± 15.50	31.24 ± 5.60	9.39 ± 0.75	6.50 ± 0.51	11.18 ± 1.76	8.63 ± 2.82	104.10 ± 12.48

[a] AUC was estimated by trapezoidal method. Values at single-dose are AUC from 0 h to infinity, calculated as AUC from 0 to 48 h plus terminal phase extrapolation to t = infinity. Values at multiple-dose steady state are AUC from 0 to 8 h according to a once-every-8-h dosing interval.

TABLE 3. Disposition pharmacokinetic parameters of levofloxacin in HIV-infected patients estimated from two-compartmental curve-fitting method

Subject no.	AUC (mg · h/liter)	MRT (h)	$t_{1/2}$ (h)	Cl_p/F (liters/h)	V_{ss} (liters)
101	25.4	7.84	5.43	13.5	106
104	25.7	9.76	6.76	13.3	130
106	40.7	10.1	7.00	8.38	84.6
107	27.5	8.84	6.12	12.4	109
110	28.9	8.90	6.17	11.8	105
Mean ± SD	29.7 ± 6.35	9.09 ± 0.88	6.30 ± 0.61	11.9 ± 2.06	107 ± 16.0

PCNONLIN version 3.0 computer program (8). The Akaike information criterion was used as an objective measure in model selection. The residual plots were also used as subjective measures of the bias of the models. A weighting function of $1/y$ was assigned to offset the non-Gaussian distribution of error in the C_p-versus-time data. The goodness of fit between the observed and predicted C_p-versus-time profiles was evaluated by the correlation coefficient (r).

Analysis of safety data included evaluation of the incidence, nature, and severity of adverse experiences and changes in baseline physical findings or laboratory results.

Statistical analysis. A paired t test was used to compare the pharmacokinetic parameter values obtained from day 1 with those obtained on day 10 of the study. $P < 0.05$ was used to determine the level of significance. Comparison of pretreatment and posttreatment physical findings and laboratory values was done via paired t tests.

RESULTS

Ten asymptomatic HIV-infected males meeting all inclusion criteria completed the study. The mean (± standard deviation) age and weight of subjects randomized to levofloxacin were 36.8 ± 13.63 years and 75.4 ± 4.4 kg, respectively. For the subjects randomized to the placebo group, the age was 32.0 ± 4.95 years and the weight was 80.1 ± 5.6 kg. The T4 helper lymphocyte count for subjects randomized to levofloxacin was 486.2 ± 115.94, and that for subjects receiving placebo was 450.6 ± 128.95. All subjects would be classified in revised Centers for Disease Control classes A1 ($n = 4$) or A2 ($n = 6$) (2).

The 24-h mean C_ps observed after administration of a single 350-mg oral dose of levofloxacin hemihydrate (day 1) and a 350-mg oral dose of levofloxacin at steady state (day 10) are plotted in Fig. 1. As shown, the two profiles are essentially parallel to each other, indicating the consistency of the pharmacokinetics of levofloxacin in these subjects. Plasma levofloxacin concentrations declined biexponentially after the observed peak concentrations following both dosing regimens, indicating two-compartment drug distribution. The observed C_{max}, T_{max}, and C_{min} for each subject are presented in Table 1. The mean C_{max} value at steady state was, on average, 1.44 times that observed after a single dose. Differences in C_{max} values between the two dosing regimens were found to be significant ($P = 0.02$). There were no significant differences between the T_{max} values on days 1 (1.00 h) and 10 (0.90 h) ($P = 0.70$). The C_{min} value at steady state was, on average, 2.12 times that observed after a single dose, and this difference was found to be significant ($P = 0.0033$). Concentrations in plasma at predose (2.38 ± 0.81 μg/ml) and 8 h postdose (2.46 ± 0.60 μg/ml) on day 10 were not different, indicating the attainment of steady state. It was also apparent that steady-state conditions had been achieved by days 6 to 7 of the study (3 to 4 days after initiation of the multiple-dose regimen), because no trend towards further increase in the C_{min} values was observed after that point.

Noncompartmental moment analysis was employed to interpret the disposition kinetics of levofloxacin after single- and multiple-dose administration of a 350-mg dose of the hemihydrate salt. The mean values for AUC, MRT, $t_{1/2}$, Cl_p/F, and V_{ss} are shown in Table 2. No significant differences in the values of any of these parameters were found when days 1 and 10 were compared, indicating that the steady-state pharmacokinetics of levofloxacin were predictable from the single-dose data in these patients.

Pharmacokinetic data were further evaluated by the compartmental nonlinear regression method. The data were better characterized by a two-compartment distribution model. Figure 2 depicts both the observed and predicted mean C_p-versus-time profiles of the subjects during the duration of the study. The predicted profile was simulated according to the mean parameter values obtained from nonlinear regression analysis of the individual subject profiles. As shown, predicted profiles

TABLE 4. Urinary concentrations and total urinary recoveries of levofloxacin after single- and multiple-dose levofloxacin hemihydrate administration

Subject no.	Single dose (day 1)							Multiple dose (day 10)				
	Urinary concn (mg/liter) at:					Total amt (mg)	Dose excreted (%)	Urinary concn (mg/liter) at:			Total amt (mg)	Dose excreted (%)
	0–2 h	2–4 h	4–8 h	8–12 h	12–24 h			0–2 h	2–4 h	4–8 h		
101	101	125	16	49	13	130	38	237	Sample lost	152	Sample lost	Sample lost
104	414	339	114	169	58	330	97	779	606	477	343	100
106	621	797	425	397	57	294	86	1,180	1,145	830	213	62
107	635	738	194	45	39	248	73	999	1,064	597	263	77
110	558	617	325	223	43	141	41	714	963	94	262	77
Mean ± SD	466 ± 222	523 ± 284	215 ± 163	177 ± 145	42 ± 18	229 ± 90	67 ± 27	782 ± 357	945 ± 238	430 ± 308	270 ± 54	79 ± 16

based on a stationary two-compartment model with short-term zero-order absorption and first-order elimination appeared to characterize all of the observed subject profiles nearly perfectly. The predicted 0- to 24-h C_p curves after administration of levofloxacin hemihydrate as single or multiple 350-mg oral doses are also depicted in Fig. 2 as connected lines. Pharmacokinetic parameter values for AUC, MRT, $t_{1/2}$, Cl_p/F, and V_{ss} obtained from the nonlinear regression analysis were similar to those obtained from the moment method (Table 3), further confirming the stability of levofloxacin pharmacokinetics in these HIV-infected subjects.

Individual urinary concentrations and the percentage of the dose excreted in the urine following a single 350-mg dose of levofloxacin or during an 8-h dosing interval at steady state are listed in Table 4. Cumulative urinary excretion of unchanged levofloxacin during the first 24 h after a single dose ranged from 38 to 97%, while urinary recovery during a dosing interval at steady state was 62 to 100%. Cl_R calculations were not performed unless urine collections were complete.

Levofloxacin was generally well tolerated by individuals with HIV infection. However, all study participants (including those on placebo) experienced adverse effects. Commonly reported adverse events included gastrointestinal (nine subjects in each treatment group), central nervous system (three subjects in each group), and dermatologic (two in levofloxacin group, four in placebo group) effects. A complete listing of adverse events experienced by study patients is presented in Table 5. Patients in both treatment groups had transient asymptomatic increases in levels of hepatic transaminases. Although the number of adverse events was higher in patients on active drug than in those on placebo (23 versus 18), there were no statistically significant differences in adverse experiences in the two groups ($P = 0.22$). No serious adverse events were reported, and no subject discontinued study participation because of an adverse event. Without a placebo control, disease-related adverse events would have been attributed to the study drug, levofloxacin.

TABLE 5. Adverse experiences of HIV-infected patients in placebo-controlled phase I study

Adverse event	No. of adverse events in:	
	Levofloxacin group	Placebo group
Gastrointestinal system		
Diarrhea, loose stools	2	1
Abdominal discomfort	1	2
Constipation	1	0
Flatulence	1	1
Indigestion	0	2
Rise in serum alkaline phosphatase level	2	0
Rise in serum aspartate aminotransferase level	1	2
Rise in serum alanine aminotransferase level	1	0
Hepatomegaly	0	1
Central nervous system, headache	3	3
Respiratory system		
Sore throat	1	0
Bronchospasm	1	0
Sinusitis	0	1
Hematologic		
Eosinophilia	1	0
Lymphocytosis	1	0
Granulocytopenia	1	0
Musculoskeletal system, myalgias	1	0
Dermatologic		
Skin rash	1	4
Dry skin	1	0
Body as a whole		
Pain	2	0
Back pain	1	0
Syncope	0	1

DISCUSSION

The purpose of this study was to evaluate the pharmacokinetics and safety of levofloxacin in patients with asymptomatic HIV infection. The absorption of this investigational fluoroquinolone antibiotic was found to proceed almost instantaneously after administration in all five subjects randomized to receive levofloxacin. Since the absorption rate of levofloxacin is rapid and absorption is essentially complete within 1 h of administration, oral absorption of levofloxacin from the tablet formulation employed in this study is not rate limited by the gastrointestinal transit process.

Compartmental curve-fitting analysis indicated that, after absorption, levofloxacin is rapidly and extensively distributed, as reflected by the short distribution phase (mean $t_{1/2\alpha}$, 1 h) and large V (mean V_{ss}, 107 liters). Levofloxacin undergoes a relatively slow elimination process (mean Cl_p/F, 11.9 liters/h; MRT, 9.09 h; mean effective $t_{1/2}$, 6.30 h; mean terminal $t_{1/2}$ [$t_{1/2\beta}$], 7.3 h), resulting in an accumulation factor of $r = 1.88$, which is essentially identical to the value estimated from $C_{\text{min day 10}}/C_{\text{min day 1}}$, 2.12.

The absorption, distribution, and elimination of levofloxacin in our asymptomatic HIV-infected subjects were very uniform, as indicated by the consistent results between days 1 and 10 as well as the goodness of fit of the entire 13-day profiles by a model with the assumption of unchanged pharmacokinetics. These results are similar to those observed after administration of lower doses of levofloxacin to normal healthy volunteers (10a). Following oral administration of single 100-mg doses to normal healthy male volunteers, peak serum levofloxacin concentrations ranged from 1.35 to 2.34 mg/liter (mean value, 1.60 mg/liter) and occurred between 0.5 and 1 h, while AUC values ranged from 8.73 to 13.24 mg · h/liter (mean, 10.82 mg · h/liter). Correcting for dose differences, these values correlated to a mean C_{max} of 5.5 mg/liter in healthy volunteers (versus 4.8 mg/liter in this study) and a mean AUC of 36.9 mg · h/liter (versus 29.0 mg · h/liter in this study). In a second study, separate groups of subjects received single and multiple 200-mg oral doses of levofloxacin (9). As in our study, the absorption and elimination of levofloxacin at steady state were predictable from the single-dose data.

Urinary concentrations of levofloxacin after single doses and at steady state were well above the MICs for susceptible pathogens (5), since, as has been observed with ofloxacin (3), a relatively large amount of the dose was excreted in the urine.

The results of this study indicate that the pharmacokinetics of levofloxacin in asymptomatic HIV-infected subjects are similar to those obtained from healthy subjects. In addition, levofloxacin appears to be safe after multiple oral doses of 350 mg every 8 h, and no dose modifications appear to be necessary in this patient population. However, the disposition of levofloxacin and other drugs may be altered in patients with more advanced HIV disease.

In a large trial comparing zidovudine (at two dosage levels) with placebo in the treatment of asymptomatic HIV-infected patients (AIDS Clinical Trials Group study 019), the incidence and severity of many adverse events were similar among patients receiving placebo and those receiving active drug (12). Adverse experiences such as headache, insomnia, malaise, and rash, rated severe by patients, were not significantly more common in zidovudine recipients. Other adverse events such as anorexia and abdominal pain occurred with similar frequency in zidovudine and placebo groups. Similarly, no differences in the incidence of anemia requiring transfusion or neutropenia between patients receiving low-dose zidovudine (500 mg/day) and placebo were noted. Patients in all three treatment groups experienced similar elevations in serum aminotransferase concentrations. Furthermore, 8 of 44 study withdrawals for medical reasons such as gastrointestinal upset, confusion, and malaise were in the placebo group.

A lack of statistically significant differences in adverse effects between treatment groups of HIV-infected patients was noted in our pharmacokinetic and safety evaluation of levofloxacin in patients with asymptomatic HIV infection. Incorporation of placebo controls in phase I trials of drugs for HIV infection should enable researchers to differentiate disease-related complaints from drug side effects early in drug development and facilitate the rapid development of effective, nontoxic dosage regimens. However, because of the increased cost and time for completion of phase I studies that would be imposed by use of a placebo control, this study design is probably only indicated for new chemical entities. Moreover, large controlled clinical trials comparing new drugs with standard HIV treatments will be required to elucidate the relative toxicity profiles of these compounds.

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